Remarks

Claims 1-29 were rejected as lacking an inventive step over U.S. Patent No. 5,451,409 to Rencher et al. ("Rencher"). Claims 1-29 were also rejected under 35 U.S.C. 103 as obvious over U.S. Patent No. 5,827,852 to Russell, et al., or U.S. Patent No. 5,648,358 to Mitra, et al. in combination with Rencher. These rejections are respectfully traversed.

The Claimed Invention

The claims define a biphasic antihistamine composition in daily oral uni-dosage or divided dosage form and a method of making and using the composition. The dosage form contains **two monophasic parts**, each having an active ingredient which is either a sedating antihistamine or a non-sedating antihistamine (p. 7, line 15 to p. 8, line 9). The claimed composition has the advantage of (1) avoiding sedating effects of sedating antihistamine during the day time and (2) taking the full advantage of sedating antihistamine in the night time (p. 9, lines 5-13), while only needing to be administered once a day. The claimed composition achieves this advantage by being formulated so that only non-sedating antihistamine is released in the day, and only sedating antihistamine is released at night (p. 8, line 10 to p. 9, line 4). Various delayed or sustained release formulations and coatings (p. 10, lines 9-25; p. 13, lines 1-13; p. 13, line 18 to p. 28, Examples 1-3) are used to achieve this release profile.

Dependent claims are drawn to compositions comprising specific sedating antihistamines (claims 2, 3, 14 and 15) or a therapeutically effective amount of an additional agent (claims 8, 19, 25, 28 and 29). The composition can have a specific release profile of the sedating or non-sedating antihistamine or the additional agent

(claims 4-7 and 16-18). The sedating or non-sedating antihistamine can be formulated into a sustained release form or a delayed release form (claims 24-27 and 29) using a at least one delayed release control polymer or at least one sustained release control polymer defined therein.

As shown in Examples 1-3, procedures are taken to ensure the biphasic feature of the composition such that the sedating antihistamine is released in the night or evening time but not released in the day time and the non-sedating antihistamine is released in the day time but not released in the night time.

Rencher

Rencher describes a single "homogeneous matrix" containing one or more actives, from which each active component is released at an appropriate rate to provide the desired activity over a period of 2 to 24, preferably 8 to 12 hours (col. 2, lines 21-27). The formulation uses a polymer blend of hydroxypropyl cellulose (HPC) and hydroxyethyl cellulose (HEC) to control the release rate of the active components (col. 1, line 60 to col. 2, line 5). It is important to note that the composition, upon administration, provides sustained; ***not delayed***, release, releasing the active component at a rate to provide the desired activity over a period of 2 to 24 hours (col. 2, lines 26-27). The active component is released immediately at an effective level and remains such over a period of 2 to 24 hours. This is clearly seen in Tables 6 and 8, which shows that the composition can release 15 to 26 percent of the active component within 30 minutes after administration.

Russell

Russell describes a pharmaceutical composition suitable for coating a drug for treating cold, cough, allergy, and flu symptoms (col. 2, lines 42-67). The active ingredient can be an antihistamine (col. 5, lines 37-42). The composition can be formed of triturate active ingredients which are **"blended together"** (col. 7, line 45 to col. 8, line 67, particularly col. 8, lines 33-35, Examples I-III). The active ingredients in a composition of a blend of triturate active ingredients do not distinguish one from another in terms of the timing and the rate of release. Therefore, the composition described in Russell, without more, would not delay the release of any of the active ingredients. It certainly cannot prevent the release of one of the active ingredient in the day time.

Mitra

Mitra describes antihistamine preparations which must contain caffeine, a stimulant (col. 2, line 24). This is the antithesis of what applicants claim: a biphasic composition that allows one to obtain the benefit of an antihistamine while sleeping, and the benefit of a non-sedating antihistamine while active. Indeed the goal of Mitra's formulation is to prevent the sleepiness due to the use of an antihistamine! (see col. 2, lines 61-67)

The Art Alone or in Combination

Rencher fails to make obvious the claimed subject matter because Rencher does not recognize the benefit of a formulation containing both a sedating antihistamine and a non-sedating antihistamine, which are released at different time periods. Moreover, Rencher teaches making a homogeneous composition of the active ingredients. In contrast, as the foregoing discussion shows, a biphasic composition as defined in any of the claims 1-29 is necessary to achi ve the release profile defined in claims of the present

application. Therefore, even if one could find a reference providing the motivation to combine a sedating with a non-sedating antihistamine, Rencher would not lead one of ordinary skill in the art to have a reasonable expectation of success of the claimed composition and method of using the composition. Further, in emphasizing a homogeneous composition, Rencher teaches away from the claimed biphasic composition.

Russell teaches forming a simple blend of triturate active ingredients while Rencher teaches forming a homogenous composition. Therefore, Russell in combination with Rencher, fails to teach one skilled in the art to make a biphasic composition, for delivery of a sedating antihistamine during the night and a non-sedating antihistamine during the day time.

Accordingly, Russell in view of Rencher would not render claims 1-29 *prima facie* obvious under 35 U.S.C. 103.

Mitra's formulation *never allows one to sleep - the caffeine is a stimulant.* If one combined Mitra's formulation into a biphasic composition, one would not achieve applicant's goal. Therefore the claimed subject matter, alone or in combination with Rencher cannot be obvious from Mitra.

Summary

In summary, none of the art motivates one skilled in the art to make a biphasic composition containing a sedating antihistamine in a first portion and a non-sedating antihistamine in a second portion where release is delayed.

The examiner has used hindsight to provide motivation. This is improper, however. It is well established that the motivation *must* come from the references

themselves. In this case, the references actually teach away from what applicants have developed. Therefore the subject matter of claims 1-29 is not obvious.

Allowance of all claims 1-29 is earnestly solicited.

Respectfully submitted,

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CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that the enclosed Response to Office Action and all documents shown as being attached is being facsimile transmitted to the U. S. Patent and Trademark Office on the date shown below.

Date: December 19, 2003

Patrea L. Pabst

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